

**Next generation macrolides for community-acquired pneumonia: Will Solithromycin rise to the occasion?**

Dr Ricardo J. José

Centre for Inflammation and Tissue Repair, UCL Respiratory, 5 University Street, London, United Kingdom, WC1E6JF

Community-acquired pneumonia (CAP) remains the leading cause of death by an infectious disease(1). Although the aetiological agent varies by geographical location and population studied in adults the most commonly isolated pathogens from adult CAP patients are bacteria. Despite the poor detection rate of CAP organisms by current microbiological techniques(2), *Streptococcus pneumoniae* continues to be the most frequently isolated pathogen(3) and is responsible for the huge burden associated with this disease. Other commonly isolated bacteria include *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*. Less regularly Enterobacteriaceae, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Moraxella Catarrhalis*, *Chlamydia psittaci* and *Coxiella Burnetii* are identified. With improved molecular diagnostics viruses are increasingly being recognised as important pathogens in CAP particularly as they predispose the host to secondary bacterial infection. Treatment of CAP therefore requires the use of antibiotics but as clinical or radiological features are not adequate to determine the aetiological agent, and due to the delay in microbiological diagnosis these have to be administered empirically. Although this is an extremely useful strategy at the early stage of treatment it is important to move to definitive less broad-spectrum treatment once a culprit pathogen has been identified to limit the emergence of antibiotic-resistant bacteria. Another important consideration in the treatment of CAP is the route of administration. Whilst intravenous formulations are useful for those who are clinically unstable or unable to take medication orally, by ensuring optimal bioavailability, this is associated with increased cost and infusion site adverse events. It is therefore important to ensure that when appropriate antibiotics are switched from intravenous to oral formulations, provided the same efficacy exists.

The antibiotic recommendations for the treatment of CAP differ by guideline and are based on knowledge of local causative pathogens, antibiotic resistance patterns and patient illness severity. The Infectious Disease Society of America/American Thoracic Society guideline recommends that in the outpatient setting previously healthy individuals living in areas of low macrolide resistance should be treated with a macrolide (e.g. erythromycin, clarithromycin or azithromycin) or doxycycline, whilst those with co-morbidities, those in areas with high macrolide resistance or those admitted to hospital should receive a respiratory fluoroquinolone (moxifloxacin or levofloxacin) or a  $\beta$ -lactam (e.g. amoxicillin, amoxicillin-clavulanate or cefuroxime) plus a macrolide. For patients requiring admission to intensive care a  $\beta$ -lactam plus azithromycin or  $\beta$ -lactam plus a respiratory fluoroquinolone, with a respiratory fluoroquinolone plus aztreonam being recommended for penicillin allergic individuals. The British Thoracic Society recommends an oral  $\beta$ -lactam (amoxicillin is preferred) or doxycycline or clarithromycin for those with low illness severity (CURB-65=0–1), a  $\beta$ -lactam (oral amoxicillin or intravenous benzylpenicillin) plus a macrolide (clarithromycin is preferred) or doxycycline or respiratory fluoroquinolone for those with moderate illness severity (CURB-65=2) and intravenous amoxicillin-clavulanate plus a macrolide or intravenous benzylpenicillin plus either levofloxacin or ciprofloxacin for those with high illness severity (CURB-65=3–5). Fluoroquinolone monotherapy is useful in the treatment of CAP(4, 5), however it is probably best reserved for those with low illness severity(6) or in those where *L. pneumophila* pneumonia is diagnosed. Furthermore, the combination of a fluoroquinolone with a  $\beta$ -lactam is advocated, but studies suggest that mortality is worse compared to when a  $\beta$ -lactam and macrolide combination is used(5–7). The empirical use of a macrolide together with a  $\beta$ -lactam antibiotic in CAP is justified by potentially 20% of CAP being caused by atypical pathogens (*L. pneumophila*, *C. pneumoniae* and *M. pneumoniae*)(3) and results in improved clinical outcomes even in the presence of drug resistant pathogens(6, 8–10).

In the last decade, in certain geographical regions, due to the abundant use of antibiotics there has been an increase in antibiotic resistant respiratory pathogens. Of concern is the increase in penicillin and macrolide-resistant *S. pneumoniae* since this is the most commonly isolated pathogen. A recent

study of 1713 *S. pneumoniae* isolates from four continents found that only 61.5% and 62.2% were sensitive to penicillin and azithromycin, respectively(11). The SENTRY antimicrobial surveillance program reported that in the United States the proportion of erythromycin-resistant *S. pneumoniae* in 2011 had increased to 55%(12). This figure is more alarming in Asia where 73% of *S. pneumoniae* isolates from a prospective surveillance study were erythromycin resistant(13). Although *S. pneumoniae* resistance to penicillin is increasing,  $\beta$ -lactam antibiotics at appropriate doses are still useful at treating infection(14, 15) and in countries such the UK and Netherlands that have a low proportion of penicillin- and erythromycin-resistant *S. pneumoniae* isolates the use of older generation antibiotics are recommended. However, macrolide-resistance is clinically important as there is evidence from a well conducted prospective study showing that macrolide-resistance is associated with treatment failure(16). However, treatment failure in this context does not appear to impact on mortality. This is confirmed by a more recent retrospective study that did not demonstrate any differences in outcome between hospitalised patients with or without macrolide-resistant *S. pneumoniae* pneumonia, but it is important to note that <5% and <50% of patients received macrolide monotherapy or combination treatment with a  $\beta$ -lactam and macrolide(17). Nevertheless, with the changing epidemiology of respiratory pathogen resistance patterns there is great need to develop novel antibiotics to treat bacterial CAP.

More recently solithromycin, a fourth generation antibacterial macrolide and first fluoroketolide, was developed. The novel chemistry, pharmacokinetics and pharmacodynamics of this drug are described in detail elsewhere(18, 19) and is beyond the scope of this article. Solithromycin is available as both an oral and intravenous preparation, is administered once daily and covers the same pathogens as other macrolides, but has the added advantage of being bactericidal rather than just bacteriostatic and is effective against bacteria which are resistant against current macrolides. In a study where 38% of *S. pneumoniae* isolates were resistant to azithromycin, 98.9% and 100% of isolates were inhibited by solithromycin at MIC values of  $\leq 0.25$  mg/L and  $\leq 1$  mg/L, respectively(11). Solithromycin also inhibited 85.3% of methicillin-sensitive *Staphylococcus aureus* isolates of which only 58.7% were sensitive to azithromycin. Additionally, in healthy subjects solithromycin doesn't significantly affect the QT interval(18, 20), which is a concern with macrolide use, such as azithromycin, and fluoroquinolones, such as moxifloxacin, and it does not appear to have the side effect profile that was seen with telithromycin, a third generation macrolide, which due to cases of drug-induced severe hepatic failure is no longer marketed(18). Another advantage is that solithromycin is more anti-inflammatory than currently used macrolides(21), which is beneficial, considering that immunomodulatory effects of macrolides is one of the suggested reasons for improved outcomes in severe CAP when combined with a  $\beta$ -lactam even in the absence of high proportions of atypical pathogens(6, 22, 23). The potential of this antibiotic to attenuate the levels of pro-inflammatory cytokines and excessive neutrophilic inflammation by inhibiting NF $\kappa$ B activity(21) may in the context of CAP lead to less lung injury as is observed with other potential immunomodulatory therapies (24, 25), however to date no clinical studies have been published looking at the efficacy of solithromycin in severe CAP, in reducing admissions for mechanical ventilation or adequately powered to detect differences in mortality.

In a phase two randomised controlled, double-blind clinical study solithromycin was compared to levofloxacin in the treatment of adult CAP. All patients had to be suitable for oral therapy and most of the included patients were in PORT class II and 27% were  $\geq 65$  years of age. Solithromycin had comparable clinical success rates to levofloxacin (84.6% versus 86.6%) at four to eleven days post treatment(26). Furthermore, it had few treatment related adverse events (29.7% versus 45.6%)(26). This led to a phase three randomised, double-blind, multi-centre non-inferiority clinical trial comparing the efficacy of oral solithromycin to oral moxifloxacin in the treatment of CAP (SOLITAIRE-

ORAL)(27). In this study solithromycin was administered for five days followed by two days of placebo whilst moxifloxacin was given for seven days, based on the duration of treatment with moxifloxacin in other CAP studies. Although this study included a greater proportion of patients classified as PORT class III, 96% of patients had a CURB-65 score  $\leq 2$ , representing a population at low risk of death from CAP(27). Solithromycin had a similar early clinical response (defined as an improvement in at least two of four symptoms, including cough, chest pain, sputum production, and dyspnoea, with no worsening in any symptom at 72 h after the first dose) and treatment failure (lack of resolution, worsening of baseline symptoms or development of new symptoms, and need for new antibacterial treatment at 5-10 days post-treatment) to moxifloxacin in the treatment of CAP, suggesting that it will be a suitable alternative to highly bacteriocidal fluoroquinolones. However, it is important to note that the number of macrolide resistant *S. pneumoniae* isolates in this study were low. It is therefore difficult to know how solithromycin will perform in a clinical setting of high macrolide resistance, however based on the surveillance data highlighted above it is predicted that solithromycin would remain effective in this setting.

Switching from intravenous antibiotics to less expensive oral formulations once the patient is clinically stable and suitable for oral therapy can reduce medication costs and potentially other associated costs by reducing length of hospitalisation and infusion-related adverse events. Recently, in the journal *Clinical Infectious Diseases*, File *et al.*(28) published the results of the SOLITAIRE-IV study which compared the efficacy of intravenous to oral switching of solithromycin to that of moxifloxacin. Patients could be switched from intravenous to oral formulations for either treatment at the discretion of the clinician but in keeping with the following guidance: improvement of baseline clinical signs and symptoms; afebrile; respiratory rate  $\leq 24$  breaths per minute, systolic blood pressure  $\geq 90$  mmHg and oxygen saturation (as determined by pulse oximetry)  $\geq 90\%$  when breathing room air(28). Both the intravenous and oral dose of solithromycin and moxifloxacin was 400 mg except for the first oral dose of solithromycin which was 800 mg. In this randomised controlled, double-blind multicentre study of 863 patients approximately 45% of patients were  $\geq 65$  years of age. This represented the significant age group that develops CAP but only 7% had a CURB-65 score  $\geq 3$ , where the predicted mortality is  $>10\%$ . This is reflected by the low mortality rate of 1.2% and 1.6% in the solithromycin and moxifloxacin groups, respectively, and does not provide evidence for the efficacy of solithromycin in those at increased risk of death. An important aspect of this study was that although patients were recruited from 147 centre in 22 countries the microbiological assessments were done centrally in one laboratory leading to a high proportion of identified pathogens. *S. pneumoniae* was the most commonly identified pathogen but again  $<5\%$  of *S. pneumoniae* isolates were macrolide-resistant. A high proportion (23%) of identified pathogens were atypical bacteria, mainly *L. pneumophila* and *M. pneumoniae*. Solithromycin was associated with more infusion site adverse events (31.3% versus 5.4%) resulting in discontinuation of treatment in 11 and 1 patients, respectively. This was not associated with the duration of intravenous treatment as this was similar between both groups. Overall, early discontinuation of treatment due to drug related adverse events was similar in both groups (5.8% and 4.2%). The clinical effectiveness determined by the early clinical response and short-term follow up visit was similar for both the solithromycin and moxifloxacin groups (79.3% versus 79.7% and 84.6% and 88.6%)(28), suggesting that switching oral to intravenous solithromycin was not inferior to moxifloxacin.

Overall, available evidence supports the use of solithromycin in the treatment of adult CAP of mild to moderate severity. Although empiric use of once daily macrolide monotherapy with solithromycin appears an attractive option it is important to consider the non-financial cost of the widespread use of new macrolides, which will likely lead to the development of solithromycin-resistant bacterial isolates. This will ultimately result in the same problem that we currently encounter with older

agents and therefore, it is likely that these new agents should be reserved for the treatment of CAP caused by microbiologically proven antibiotic-resistant bacteria without evidence of clinical improvement where current guideline recommended regimens are failing.

Despite current data indicating that solithromycin is non-inferior to fluoroquinolones in the treatment of CAP, the US Food and Drug Administration (FDA) has not approved the use of solithromycin(29). It has acknowledged the efficacy of solithromycin for the treatment of bacterial CAP but a major concern to the licensing of solithromycin is the potential risk of severe idiosyncratic drug induced liver injury and has recommended that the manufacturer should conduct a clinical safety study that exposes 9000 individuals to solithromycin. Such a study will be expensive and time-consuming, and it is therefore unknown if this next step will be undertaken by the manufacturer. The development of novel antibiotics for the treatment of CAP is an unmet need and once reassurances are provided regarding severe hepatotoxicity we may see the rise of solithromycin.

## References:

1. World Health Organisation. Global burden of disease: 2004 update. 2008. Available at: [http://www.who.int/healthinfo/global\\_burden\\_disease/GBD\\_report\\_2004update\\_full.pdf](http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf). Accessed November 11, 2014.
2. José RJ, Brown JS. Predicting bacteraemia or rapid identification of the causative pathogen in community acquired pneumonia: where should the priority lie? *EUR. RESPIR. J.* 2016;48(3):619–22.
3. Torres A, Blasi F, Peetermans WE, et al. The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review. *EUR. J. CLIN. MICROBIOL. INFECT. DIS.* 2014;33(7):1065–79.
4. Vardakas KZ, Siempos II, Grammatikos A, et al. Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. *CMAJ* 2008;179(12):1269–77.
5. Bratzler DW, Ma A, Nsa W. Initial Antibiotic Selection and Patient Outcomes: Observations from the National Pneumonia Project. *CLIN. INFECT. DIS.* 2008;47(S3):S193–S201.
6. Rodrigo C, Mckeever TM, Woodhead M, et al. Single versus combination antibiotic therapy in adults hospitalised with community acquired pneumonia. *THORAX* 2013;68(5):493–5.
7. Vardakas KZ, Trigkidis KK, Falagas ME. Fluoroquinolones or macrolides in combination with  $\beta$ -lactams in adult patients hospitalized with community acquired pneumonia: a systematic review and meta-analysis. *CLIN. MICROBIOL. INFECT.* 2016.
8. Falagas ME, Siempos II, Bliziotis IA, et al. Impact of initial discordant treatment with beta-lactam antibiotics on clinical outcomes in adults with pneumococcal pneumonia: a systematic review. *MAYO CLIN. PROC.* 2006;81(12):1567–74.
9. Sligl WI, Asadi L, Eurich DT, et al. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. *CRIT. CARE MED.* 2014;42(2):420–32.
10. Restrepo MI, Mortensen EM, Waterer GW, et al. Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. *EUR. RESPIR. J.* 2009;33(1):153–9.
11. Farrell DJ, Flamm RK, Sader HS, et al. Results from the Solithromycin International Surveillance Program (2014). *ANTIMICROB. AGENTS CHEMOTHER.* 2016;60(6):3662–8.
12. Jones RN, Sader HS, Mendes RE, et al. Update on antimicrobial susceptibility trends among *Streptococcus pneumoniae* in the United States: report of ceftaroline activity from the SENTRY Antimicrobial Surveillance Program (1998–2011). *DIAGN. MICROBIOL. INFECT. DIS.* 2013;75(1):107–109.
13. Kim SH, Song J-H, Chung DR, et al. Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *ANTIMICROB. AGENTS CHEMOTHER.* 2012;56(3):1418–26.
14. Chiou CC. Does penicillin remain the drug of choice for pneumococcal pneumonia in view of emerging in vitro resistance? *CLIN. INFECT. DIS.* 2006;42(2):234–7.
15. Postma DF, Werkhoven CH van, Elden LJR van, et al. Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults. *N. ENGL. J. MED.* 2015;372(14):1312–1323.

16. McGeer D, Green AK, Low DE, et al. Macrolide Resistance in Bacteremic Pneumococcal Disease: Implications for Patient Management. CLIN. INFECT. DIS. 2006;43(4):432–438.
17. Cilloniz C, Albert RK, Liapikou A, et al. The Effect of Macrolide Resistance on the Presentation and Outcome of Patients Hospitalized for *Streptococcus pneumoniae* Pneumonia. AM. J. RESPIR. CRIT. CARE MED. 2015;191(11):1265–1272.
18. Fernandes P, Martens E, Bertrand D, et al. The solithromycin journey—It is all in the chemistry. BIOORG. MED. CHEM. 2016;24(24):6420–6428.
19. Zhanel GG, Hartel E, Adam H, et al. Solithromycin: A Novel Fluoroketolide for the Treatment of Community-Acquired Bacterial Pneumonia. DRUGS 2016;76(18):1737–1757.
20. Darpo B, Sager PT, Fernandes P, et al. Solithromycin, a novel macrolide, does not prolong cardiac repolarization: a randomized, three-way crossover study in healthy subjects. J. ANTIMICROB. CHEMOTHER. 2016:dkw428.
21. Kobayashi Y, Wada H, Rossios C, et al. A novel macrolide solithromycin exerts superior anti-inflammatory effect via NF-κB inhibition. J. PHARMACOL. EXP. THER. 2013;345(1):76–84.
22. Brown JS, Hill AT. Macrolides and pneumonia. THORAX 2013;68(5):404–5.
23. Gattarello S, Borgatta B, Solé-Violán J, et al. Decrease in mortality in severe community-acquired pneumococcal pneumonia: impact of improving antibiotic strategies (2000-2013). CHEST 2014;146(1):22–31.
24. Jose RJ, Williams AE, Mercer PF, et al. Regulation of Neutrophilic Inflammation by Proteinase-Activated Receptor 1 during Bacterial Pulmonary Infection. J. IMMUNOL. 2015;194(4):333–337.
25. Müller-Redetzky H, Lienau J, Suttrop N, et al. Therapeutic strategies in pneumonia: going beyond antibiotics. EUR. RESPIR. REV. 2015;24(137).
26. Oldach D, Clark K, Schranz J, et al. Randomized, double-blind, multicenter phase 2 study comparing the efficacy and safety of oral solithromycin (CEM-101) to those of oral levofloxacin in the treatment of patients with community-acquired bacterial pneumonia. ANTIMICROB. AGENTS CHEMOTHER. 2013;57(6):2526–34.
27. Barrera CM, Mykietiuk A, Metev H, et al. Efficacy and safety of oral solithromycin versus oral moxifloxacin for treatment of community-acquired bacterial pneumonia: a global, double-blind, multicentre, randomised, active-controlled, non-inferiority trial (SOLITAIRE-ORAL). LANCET INFECT. DIS. 2016;16(4):421–430.
28. File TM, Rewerska B, Vucinić-Mihailović V, et al. SOLITAIRE-IV: A Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of Intravenous-to-Oral Solithromycin to Intravenous-to-Oral Moxifloxacin for Treatment of Community-Acquired Bacterial Pneumonia. CLIN. INFECT. DIS. 2016;63(8):1007–16.
29. Cempra Inc. Cempra Receives Complete Response Letter From FDA For Solithromycin NDAs. 2016. Available at: <http://investor.cempra.com/releasedetail.cfm?ReleaseID=1005708>. Accessed December 29, 2016.